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AF/1624/15

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Rosen et al.	
Application No.: 09/937,192	Group Art Unit: 1624
Filed: 9/21/2001	Examiner: B. Kifle
Title: Methods and Compositions for Degradation and for Inhibition of HER-Family Tyrosine Kinases	Confirmation No: 6277
Attorney Docket No.: MSK.P-038	
Customer No.: 021121	

Commissioner for Patents

PO Box 1450

Alexandria, VA 22313-1450

APPEAL BRIEF TRANSMITTAL

Dear Sir:

Applicants enclose in triplicate the Brief for Appellant in the above-captioned case along with Exhibits A through O. The fee for the filing of the brief is enclosed.

The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account 15-0610.

Respectfully submitted,

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BRIEF FOR APPELLANT

This brief is filed in support of Applicants' Appeal from the final rejection mailed June 11, 2003. Consideration of the application and reversal of the rejections are respectfully urged.

Real Party in Interest

The real party in interest is the assignee Sloan-Kettering Institute for Cancer Research. The application is licensed to Conforma Therapeutics Corporation.

Related Appeals and Interferences

An appeal is pending in Serial No. 09/960,665 which claims priority from this application. The Appeal Brief has been filed in that case. This separate appeal is pursued because the Examiner has made rejections in this case not made in the other case he is handling.

I hereby certify that this paper and any attachments named herein are being deposited with the US Postal Service as first-class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on December 15, 2003.

Marina T Larson

Marina T. Larson, PTO Reg. No. 32,038

December 15, 2003
Date of Signature

Status of Claims

Claims 3, 4, 6 and 9-34 are pending in this application. Claims 1, 2, 5, 7, and 8 have been cancelled. No other claims have been presented in this application.

Status of Amendments

All amendments prior to Appeal have been entered.

Summary of Invention

The claims of this application relate to bifunctional molecules comprising two linked-together ansamycin moieties. In the bifunctional molecules, the ansamycin moieties can bind to hsp90 in the pocket to which ansamycin antibiotics bind, and the bifunctional molecules are effective for inducing the degradation and/or inhibition of proteins, including HER-family tyrosine kinases in the cells with which they interact. The compositions of the invention can be used for treatment of cancers, including HER-positive cancers with reduced toxicity, since these compounds potently kill cancer cells but affect fewer proteins than geldanamycin, an ansamycin antibiotic, when used by itself. This activity of hsp-binding compounds is not limited to to HER-kinase. Thus, the compositions of the invention can be used theraeutically against a broad range of cancers expressing other proteins degraded in the presence of hsp90 binding molecules.

In the pending claims, claims 3-11 are directed to bifunctional chemical compounds. Claims 12 and 24-29 are directed to a method for destruction of cells expressing a HER-family kinase using a compound of the type set forth in the composition claims. Claims 13-23 and 30-34 are directed to a method for treating cancer. Of these claims 14, 21-23 and 30-34 are directed to treating cancers expressing a HER-family kinase.

Issues on Appeal

(1) Whether claims 3, 4, 6, 9-17 and 27-34 meet the definiteness requirements of 35 USC § 112, second paragraph?

(2) Whether claims 12-30 are enabled by the teaching in the specification?

Applicants submit that both of these issues should be answered in the affirmative, and the rejection of the claims reversed in full.

Grouping of Claims

With respect to the indefiniteness rejection, claim 9 is argued as a separate group, and does not stand or fall with claims 3, 4, 6, 10-17 and 27-34 are argued as a single group for purposes of the indefiniteness rejection and these claims stand or fall together.

With respect to the enablement rejection there are three groups that do not stand or fall together.

(a) Claims 12 and 24-29 which are directed to a method for destruction of cells expressing a HER-family kinase using a compound of the type set forth in the composition claims are argued as a first group.

(b) Claims 13 and 15-20 which are directed to a method for treating cancer but are not limited to cancers expressing a HER-family kinase; and

(c) Claims 14, 21-23 and 30 which are directed to treating cancers expressing a HER-family kinase.

Argument

The Indefiniteness Rejection

Claims 3, 4, 6, 9-17 and 27-34 stand rejected under 35 USC § 112, second paragraph, as indefinite. The Examiner asserts that the meaning of the term "ansamycin antibiotic" would not be clear to a person skilled in the art. Applicants respectfully disagree and request reversal of this rejection.

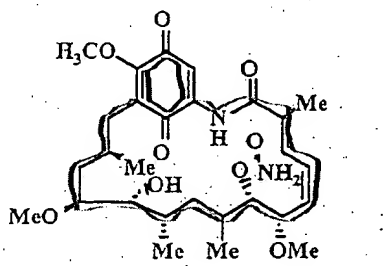
As a first matter, in claim 9, both the ansamycin moieties are identified as being geldanamycin moities. The Examiner has expressly stated that the scope of geldanamycin is known, and claims 18 and 24 which contain the same limitation are not rejected on this ground. Therefore the application of this rejection to claim 9 is plainly in error and should be reversed.

35 USC § 112, second paragraph, creates a requirement that an Applicant must present claims "particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.," The "essence of that requirement is that the language of the claims must make it clear what subject matter they encompass." *In re Hammack*, 166 USPQ 204 (CCPA 1970). This requirement has usually been viewed from the perspective of a potential infringer, "so that they may more readily and accurately determine the boundaries of protection involved and evaluate the possibility of infringement and dominance." 166 USPQ at 208.

Applicants respectfully submit that the term "ansamycin antiobiotic" is a recognized term of art, as is apparent from searches on the internet or in the USPTO full text search engine. For example, US Patent No. 4,247,462, entitled "Ansamycin Antibiotic" states that:

> The ansamycins constitute a class of antibiotics characterized by an aliphatic bridge linking two nonadjacent positions of an aromatic nucleus. The rifamycins and streptovaricins are well known members of this class of antibiotics. The chemistry of the ansamycin antibiotics is reviewed by K. L. Rinehart, Jr. and L. S. Shield in Progress in the Chemistry of Organic Natural Products, published by Springer-Verlag, Vienna-New York (1976).

See also, US Patent No. 4,738,958 entitled "Ansamycin antibiotic and its use as a medicament." When one takes the structure of geldanamycin for example, these definitions are applied as follows:



Geldanamycin (GM)

where the organic nucleus is indicated in red and the ansa ring is indicated in green.

The Examiner has criticized this definition, stating without support or explanation in the Official Action of June 11, 2003 that the application of this definition to geldanamycin (a recognized member of the ansamycin family) shows the definition to be flawed because "no aromatic nucleus is present (the quinone is not aromatic) and no aliphatic bridge [is present] (an aliphatic group does not have a nitrogen in it)." (Office Action, page 2)

The definition provided by Applicants conforms to the definitions and the usage in the art. The term "anasmycin antibiotic" is used in patents and in the literature to describe compounds such as geldanamycin, herbimycin A (both of which are mentioned on page on Page 1 line 26 and Page 4, line 13 of the application). The fact that it is used without further explanation refutes the Examiner's position that the artisan does not understand the meaning of the term. Applicants further enclose two additional publications, US Patent No. 3,954,737 (Ex. A) and K. Rinehart, *Accounts of Chem. Res.* 5: 57-64 (1972) (Ex. B), both of which expressly state the same definition previously provided by Applicants. To the extent that this definition might not meet exact chemical nomenclature, it is nevertheless the definition used in the art and is therefore controlling. However, the Examiner's unsupported assertions with respect to the application of the definition are in error as well.

First, the Examiner's unsupported contention that the definition must be wrong because the term "aliphatic" does not encompass nitrogen containing groups is not only inconsistent with the usage in the art relating to ansamycins, it is inconsistent with the ordinary meaning of the term in the chemical arts generally. Specifically, one online glossary defines "aliphatic" as "An organic compound that does not contain ring structures." http://antoine.frostburg.edu/chem/senese/101/glossary/a.shtml#aliphatic. (Ex. C) Another defines it as "pertaining to any member of one of the major groups of organic compounds, those having a straight or branched chain structure." http://www.mercksource.com/pp/us/cns/cns_hl_dorlands.jspzQzpgzEzzSzppdocszSzuszSzcommonzSzdorlandszSzdorlandzSzdmd_a_24zPzhtm#918702. (Ex. D). Yet another defines it as "of, relating to, or being an organic compound having an open-chain structure (as an alkane)."

http://www.m-w.com/cgi-bin/dictionary?book=Dictionary&va=aliphatic. (Ex. E) In none of these definitions is there any limitation that would exclude nitrogen or other non-carbon atoms.

The Examiner also asserts without explanation or support that the quinone is not aromatic. Again, this argument is inconsistent with the usage in the art as exemplified by Rinehart and other documents of record. Furthermore, dictionary definitions of "quinone" refer to it as an aromatic. For example, one online dictionary defines quinone as

> Any of a class of aromatic compounds found widely in plants, especially the yellow crystalline form, C6H4O2, used in making dyes, tanning hides, and photography.

http://dictionary.reference.com/search?q=quinone. (Ex. F) Another states that:

> This is a general name for aromatic compounds that have two atoms of hydrogen replaced by two atoms of oxygen, usually in the para position.

http://www.drumlib.com/dn/qu.htm. (Ex. G) Accordingly, Applicants submit that the rejection under § 112, second paragraph should be reversed, because there is no reason to imagine that a person skilled in the art would have any difficulty determining the scope of the claims.

The Enablement Rejection

Claims to destruction of cells

Claims 12 and 24-29 are directed to a method for destruction of cells expressing a HER-family kinase using a compound of the type set forth in the composition claims. The Examiner has rejected these claims as lacking enablement, stating that "undue experimentation is required to use compounds of the instant claims to treat cancers generally or those which over express a HER-family kinase." These claims, however, recite only killing cells that express a HER-family kinase, and not the treatment of cancer. Thus, the basis for the rejection of these claims under the logic asserted in the application is unclear. The Examiner has not offered any reasons why the killing of cells is subject to doubt.

The Examiner has also rejected those claims that refer to the treatment of cancer, but do not recite a specific cancer as lacking enablement. These claims are properly considered in two groups, first claims 13 and 31-35 which do not specifically recite that the cancer is one

that expresses HER kinase, and claims 36 which does make this recitation, although the Examiner has refused to give separate consideration on this basis.

The basis for the enablement rejection is the Examiner's statement that the claims "are drawn to the treatment of cancer generally," and his unsupported assertion that "no compound has ever been found that can treat cancers generally." The basis for this argument is largely that the Examiner is classing cancer therapy with perpetual motion machines and assumes in assessing enablement that it is inherently unbelievable that a cancer therapy could work generally. Such may have been the case when *In re Buting,* 163 USPQ 689 (CCPA 1969) cited by the Examiner, was decided in 1969, but the art and the law have progressed since then. The notion of automatic unbelievability is no longer credited. Indeed, as the Board of Appeals noted in 1987 in *Ex parte Rubin*, 5 USPQ2d 1461, 1462 (POBAI 1987), "'contemporary knowledge in the art ' has far advanced since the days when the any statement of utility in treating cancer was per se 'incredible.'" Here, the Examiner has not offered any reasoning as to why the assertions of general utility in this application, given the suggested mechanism of action. As such, the Examiner has failed to meet the burden discussed in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971), where it is noted that:

> a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond to those used in describing and defining the subject matter sought to be patents *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112, *unless* there is a reason to doubt the objective truth of the statements contained therein, which must be relied upon for an enabling disclosure.

An over thirty-year-old case, discussing the state of the art at that time, is not a reason to doubt the truth of the asserted utility here.

Furthermore, Applicants have submitted evidence showing that a monomeric ansamycin compound, 17-allylamino-geldanamycin (17-AAG), which is mentioned in the specification on Page 8, line 15 and other hsp90 inhibitors are efficacious in a variety of tumor types including breast cancer, ovarian cancer, pancreatic cancer and gastric cancer (the cancer types specifically mentioned on Page 8, lines 9-11 of the application), other HER kinase overexpressing tumors, and tumors which do not over express HER kinase. For example, Yang

et al. (Exhibit H), report inhibition of glioma (brain tumor) cells with 17-AAG. Okabe et al. (Exhibit I) reports *in vivo* activity of herbimycin A (an ansamycin antibiotic) against leukemia cells. Kelland *et al* (Exhibit J, JNCI 91: 1940, 1999) achieved tumor cytostasis in two human colorectal carcinomas, HT29 and BE for the duration of drug treatment with 17-AAG. Burger *et al* (Exhibit K Proc. AACR, 41: Abstract # 2844, 2000) reported potent effects of 17-AAG against a melanoma xenograft and, interestingly, preliminary data from the London arm of the 17-AAG trial indicates that melanoma (2/6 objective responses) may be a responsive tumor (Exhibit L Banerji *et al*, Proc. ASCO, Abstract # 326, 2001) 17-AAG has also been used in studies with prostate cancers, and it has been shown that this administration resulted in dose-dependent inhibition of androgen-dependent and -independent prostate cancer xenografts. (Exhibit M Solit et al., *Clin. Cancer Res.* 8: 986-993, 2002). 17-AAG has also been shown to enhance paclitaxel-mediated cytotoxicity in lung cancer cells (Exhibit N Nguyen et al, *Ann. Thorac. Surg.* 72: 371-379, 2001); and to modulate metastasis phenotypes in non-small cell lung cancer (Exhibit O Nguyen et al., *Ann. Thorac. Surg.* 70: 1853-60, 2000). Thus, the efficacy of compounds that bind to the hsp90 receptor span a wide range of unrelated cancers, thereby refuting the Examiner's statement that generalized cancer therapy is inherently unbelievable.

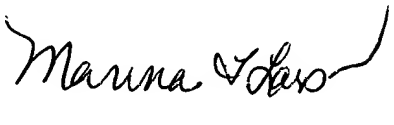
Despite repeated requests, the Examiner has never commented on these articles. Because of this, Applicants are unable to address here any reasons he may have for deeming the articles insufficient. Applicants do note, however, that the fact that the articles are dated after the filing date of this application is not relevant, since tests performed after the filing date can be used to demonstrate the enablement, and the efficacy of that which was disclosed. Furthermore, while the tests described in the articles do not utilize the specific bifunctional compounds used in the present invention, they use monomeric hsp-binding compounds which could be coupled as quasi dimers, and the use of such dimers would be within the scope of the rejected claims. The Examiner has not offered any reasons as to why a person skilled in the art would doubt the utility of these dimers.

For these reasons, the rejection for lack of enablement should be reversed.

Conclusion

In light of the foregoing, favorable consideration of the application and reversal of the rejections of record are respectfully urged.

Respectfully submitted,



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APPENDIX
CLAIMS ON APPEAL

3. A chemical compound comprising first and second hsp-binding moieties which bind to the pocket of hsp90 with which ansamycin antibiotics bind, said binding moieties being connected to one another by a linker, wherein the first and second hsp-binding moieties are each an ansamycin antibiotic.

4. The chemical compound of claim 3, wherein at least one of the hsp-binding moieties is geldanamycin.

6. The chemical compound of claim 4, wherein the linker has a length of 4 to 7 carbon atoms.

9. The chemical compound of claim 3, wherein the first and second hsp-binding moieties are geldanamycin.

10. The chemical compound of claim 9, wherein the linker has a length of 4 to 7 carbons atoms.

11. The chemical compound of claim 10, wherein the linker has a length of 4 carbon atoms.

12. A method for destruction of cells expressing a HER-family tyrosine kinase, comprising administering to the cells a chemical compound comprising first and second hsp-binding moieties which bind to the pocket of hsp90 with which ansamycin antibiotics bind, said binding moieties being connected to one another by a linker, wherein the first and second hsp-binding moieties are each an ansamycin antibiotic.

13. A method for treating cancer in a patient suffering from cancer, comprising administering to the patient a therapeutic composition comprising a chemical compound comprising first and second hsp-binding moieties which bind to the pocket of hsp90 with which ansamycin antibiotics bind, said binding moieties being connected to one another by a linker, wherein the first and second hsp-binding moieties are each an ansamycin antibiotic.

14. The method of claim 13, wherein the cancer is an HER-positive cancer.

15. The method according to claim 13, wherein at least one of the hsp-binding moieties is geldanamycin.

16. The method according to claim 15, wherein the linker has a length of 4 to 7 carbon atoms.

17. The method according to claim 16, wherein the linker has a length of 4 carbon atoms.

18. The method according to claim 13, wherein the first and second binding moieties are geldanamycin.

19. The method according to claim 18, wherein the linker has a length of 4 to 7 carbon atoms.

20. The method according to claim 19, wherein the linker has a length of 4 carbon atoms.

21. The method according to claim 14, wherein at least one of the hsp-binding moieties is geldanamycin.

22. The method according to claim 21, wherein the linker has a length of 4 to 7 carbon atoms.

23. The method according to claim 22, wherein the linker has a length of 4 carbon atoms.

24. The method according to claim 12, wherein the first and second binding moieties are geldanamycin.

25. The method according to claim 24, wherein the linker has a length of 4 to 7 carbon atoms.

26. The method according to claim 25, wherein the linker has a length of 4 carbon atoms.

27. The method according to claim 12, wherein at least one of the hsp-binding moieties is geldanamycin.

28. The method according to claim 27, wherein the linker has a length of 4 to 7 carbon atoms.

29. The method according to claim 28, wherein the linker has a length of 4 carbon atoms.

30. The method of claim 13, wherein the cancer is one in which the cancer cells overexpress a HER-family kinase.

31. The method of claim 13, wherein the cancer is breast cancer.

32. The method of claim 13, wherein the cancer is ovarian cancer.

33. The method of claim 13, wherein the cancer is pancreatic cancer.

34. The method of claim 13, wherein the cancer is gastric cancer.